PFOS and PFOA

Toxicological Overview

**Key Points**

**Kinetics and metabolism**
- PFOS and PFOA are readily absorbed following ingestion
- Following absorption PFOS and PFOA are mainly distributed to the serum and liver
- Both are only very slowly eliminated from the body in humans

**Health effects of acute exposure**
- There are insufficient data available on acute toxicity in humans to draw conclusions
- Dermal or ocular exposure to PFOS or PFOA may cause irritation
- Animal studies suggest both PFOS and PFOA are moderately toxic following ingestion, causing effects on the liver and gastrointestinal tract

**Health effects of chronic exposure**
- Toxic effects following repeated oral exposure includes effects on the liver, gastrointestinal and thyroid hormone effects
- Hepatotoxicity is the main effect reported in animals exposed to PFOS or PFOA via ingestion
- A small number of occupational studies have reported an association between exposure to PFOS or PFOA and several forms of cancer.
- Animals studies suggest that both PFOS and PFOA may be carcinogenic at relatively high dose levels
  - Animal studies indicate no marked effects on reproductive function nor development at levels below those producing maternal toxicity

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Toxicological Overview

Summary of Health Effects

Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are members of a group of chemicals known as perfluorinated chemicals (PFCs). They are essentially non-volatile and exposure is most likely via the oral route in contaminated food or water.

PFOS and PFOA are well absorbed orally and are very slowly eliminated from the body in humans with a half life of approximately nine and four years, respectively.

There are no data to assess the acute toxicity following high exposure in humans. Animal data suggest that they have moderate acute oral toxicity with effects on the gastrointestinal tract and liver. Animal data suggest that they are mild skin and eye irritants.

A range of toxic effects has been seen in animals following chronic exposure including effects on the liver, gastrointestinal tract and thyroid hormone levels.

Neither PFOS or PFOA have any mutagenic properties. They have both been shown to induce tumours in studies in animals at relatively high doses. A threshold can be assumed for the carcinogenic effects.

There are no data available on the reproductive and developmental effects of PFOS or PFOA in humans. Developmental effects have been reported in the offspring of animals exposed to PFOS or PFOA. These effects were often observed at doses that caused maternal toxicity.
**Kinetics and Metabolism**

PFOS and PFOA are readily absorbed by the gastrointestinal tract following oral exposure. They are distributed predominantly in the serum and liver. Neither PFOS or PFOA are metabolised to any significant extent and PFOS is slowly excreted predominantly in urine and to a lesser extent, faeces [1-3], whereas the elimination of PFOA is sex related in the rat, with females more rapidly eliminating PFOA in the urine than males, largely due to active renal excretion. However, in humans renal clearance of PFOA is almost negligible in both sexes [1-6].

The estimated half-lives for PFOS and PFOA in humans are 8.7 and 3.8-4.4 years, respectively [1, 2, 4, 5].

In animals both PFOS and PFOA can readily cross the placenta, although in humans they may not cross into fetal circulation completely [5]. Traces of PFOS and PFOA have been detected in human milk [7].

**Sources and Route of Human Exposure**

The main routes of exposure to PFOS and PFOA are via inhalation of contaminated air or by ingestion of contaminated water or food. Both compounds are essentially non-volatile and the general public would not be expected to be exposed via inhalation [6].

PFOA and PFOS may be released into the environment during their production [8]. Other potential sources of emissions of PFOS to the environment include releases into the atmosphere following certain domestic or commercial uses of PFOS or PFOS containing products, leachates from landfills and run-off from various applications [8]. The degradation of other fluorocarbon compounds can also lead to the release of PFOS or PFOA into the environment [8, 9]. However, the major global producer ceased production in 2002 due to concerns about persistence in the environment. Furthermore, essentially all uses were banned in the EU in June 2008 under Directive 2006/122/EC in relation to restrictions on the on the marketing and use of PFOS.

PFC’s are extremely heat, chemically and biologically stable and hence are persistent in the environment. The recent fire at the Buncefield oil depot has increased concerns over the potential for PFOS to enter drinking water supplies as a result of environmental discharges from fire-fighting activities [10]. However, data from the Drinking Water Inspectorate (DWI) has not indicated the presence of levels in drinking water that would give rise to any health concern.

There have been several reports of PFOS and PFOA being identified in fish and in other foods. Therefore, The Food Standards Agency (FSA) analysed food group samples from the 2004 Total Diet Study (TDS) for a range of fluorinated chemicals. The study models the typical UK diet. PFOS was detected at a concentration above the limit of detection in potatoes, canned vegetables, eggs and sugars and preserves food groups. PFOA was only detected in the potato group. The estimated high level adult intakes of PFOS and PFOA from the whole diet in 2004 were 0.03-0.2 µg/kg bw/day and 0.003-0.1 µg/kg bw/day, respectively [7]. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that the estimated intake for PFOA was not of concern regarding human health [4]. However, it was noted that some individuals may exceed the PFOS recommended TDI of 0.3 µg/kg bw/day. The COT concluded that there were considerable uncertainties in the dietary intake estimates, and therefore the potential exceedances do not indicate immediate toxic concern [5].
PFOS concentrations measured in the particulate phase of air in an urban area in the UK are extremely low, being in the range of 0.0009-0.051 ng/m³, in 2005 [11].

Individuals who work in industries that produce or use PFOS or PFOA may be exposed to higher levels compared with the general population. PFOS has been measured in human blood samples taken from manufacturing workers (0.80 - 1.32 ppm) and in trace amounts in the general population (35-53 ppb) [1].
Health Effects of Acute / Single Exposure

**Human Data**

**Inhalation**

**PFOS and PFOA**
There are no data on acute toxicity of PFOS or PFOA following inhalation in humans.

**Ingestion**

**PFOS and PFOA**
There are no data on acute toxicity of PFOS or PFOA following ingestion in humans.

**Dermal / ocular exposure**

**PFOS and PFOA**
There are no data on acute toxicity of PFOS or PFOA following dermal or ocular exposure in humans.

**Animal and In-Vitro Data**

**Inhalation**

**PFOS**
Rats were exposed to high concentrations of PFOS dust in air (1.9-46 mg/L) for 1 hour and showed signs of emaciation, nasal discharge, stained urogenital region, breathing disturbances and general poor condition. Decreased body weight, discoloration of the lung, liver and small intestine were also noted. The LD$_{50}$ for PFOS was 5.2 mg/L [1, 3].

**PFOA**
There are no data available on the health effects of acute inhalation exposure to PFOA in animals.

**Ingestion**

**PFOS**
PFOS has shown moderate acute toxicity by the oral route. The oral LD$_{50}$ in rats is 230 and 270 mg/kg bw (range 160-340 and 200-370 mg/kg bw) for males and females, respectively. Signs of toxicity included hypoactivity, stained urogenital region, decreased limb tone and ataxia, stomach distension and lung congestion [3, 5].

**PFOA**
Several acute oral studies in animals indicate that PFOA is moderately toxic [4]. The oral LD$_{50}$ in rats ranged between 430-680 mg/kg bw. Higher doses of PFOA (concentration not given) have been reported to cause enlarged livers, gastrointestinal irritation and weight loss in rats [3]. The guinea pig appears more sensitive with an acute LD$_{50}$ of approximately 200 mg/kg bw [3, 4].
Dermal / ocular exposure

**PFOS**
In animal studies PFOS has been shown to be mildly irritating to the eyes and non-irritating to the skin of rabbits, administered 0.5 g and 0.1g PFOS for skin and eye irritation, respectively [1, 3].

**PFOA**
PFOA caused mild skin irritation in rabbits. Rats were less sensitive than rabbits [11].
Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

PFOS
There are limited epidemiological data on PFCs. Initial analysis showed no consistent correlation between exposure to PFOS and haematological or clinical chemistry parameters. After adjusting for confounding factors PFOS was significantly correlated with thyroid hormone (T3) and cholesterol concentrations, although it was stated that there were several limitations to these studies [1, 3].

Ingestion

PFOS and PFOA
There are currently no data available on the health effects of chronic ingestion of PFOS or PFOA in humans.

Genotoxicity

PFOS and PFOA
There are currently no data available on the genotoxicity of PFOS or PFOA in humans.

Carcinogenicity

PFOS
One study reported an association of PFOS exposure and the incidence of bladder cancer and an increased risk of neoplasm of the male reproductive and gastrointestinal tract. However these workers were potentially exposed to benzidine, a known bladder carcinogen. Using an ‘episode of care’ analysis (a series of health care services provided throughout a disease), those that had been in long-term employment and were considered highly exposed according to their job, had an increased risk of cancer of the gastrointestinal, biliary and reproductive tract compared to unexposed controls [1, 3]. The COC considered that it was not possible to draw any definite conclusions from these data.

PFOA
Two occupational studies carried out on workers at a 3M plant showed an elevated standardised mortality rate for prostate cancer, whereas only one of the studies reported increased pancreatic and large intestinal cancers, although the increases noted were small. A smaller study also reported a significant increase of bladder and kidney cancer [3]. The COC considered that none of the effects repeated were significant for risk assessment.

Reproductive and developmental toxicity

PFOS and PFOA
There are no data to assess the reproductive toxicity of PFOS or PFOA in humans.
Animal and In-Vitro Data

Inhalation

PFOS and PFOA

There are currently no data available on the health effects of chronic inhalation of PFOS or PFOA in animals.

Ingestion

PFOS

Several studies have been carried out in which hepatotoxicity was reported following dietary administration of PFOS to rats or monkeys.

In a 90-day study, rats were administered 0, 2, 6, 18, 60 or 200 mg/kg bw/day PFOS in the diet. At the two lowest doses, an increased relative and absolute liver weight was reported whereas the highest three doses caused mortality [1, 5]. Similarly, a study in which rats were exposed to up to 1.4 mg/kg bw/day for 14 weeks in the diet also reported an increase in relative and absolute liver weight at the top dose, although in a parallel study where rats were exposed to up to 1.6 mg/kg bw/day for 4 weeks only relative liver weight was significantly affected [1, 3, 5]. Re-analysis by COT derived a BMDL10 of 0.2 mg/kg bw/day for increased relative liver weight, the most sensitive end-point in this study.

Rats given PFOS (3 mg/kg bw/day ) by gavage for 28 days showed an increased relative liver and kidney weight and a reduced body weight [3].

In a 90-day study, rhesus monkeys were given 0, 0.5, 1.5 or 4.5 mg/kg bw/day by gavage. The highest dose caused mortality in all animals, due to gastrointestinal toxicity. The other two groups also showed signs of gastrointestinal effects but they were less severe. In another study Cynomolgus monkeys were given capsulated PFOS (0.03, 0.15 or 0.75 mg/kg bw/day ) by gavage for 26 weeks. Two animals given the highest dose died probably due to pulmonary inflammation and necrosis or hyperkalaemia. The remaining animals in this group all had significantly increased relative liver weights, and females also had increased absolute liver weights. Other adverse liver effects were also noted such as centrilobular vacuolisation and hypertrophy [1, 3]. A number of clinical chemistry effects were noted in the treated group including reduced total cholesterol and effects on thyroid hormones, the latter being the most sensitive effect (decreased serum T3 levels). The NOAEL was considered to be 0.03 mg/kg bw/day.

PFOA

Mice given PFOA (up to 200 mg/kg bw/day) for 28 days showed signs of muscular weakness and roughened fur. Absolute and relative liver weights were increased in all groups in both males and females except the lowest group (2 mg/kg bw/day) in which only females were affected. Treatment related liver toxicity was also observed. Rats given up to 30000 ppm PFOA for 28 days (equivalent doses not given) or up to 1000 ppm for 90 days (64 mg/kg bw/day in males and 76 mg/kg bw/day females) again had an increased liver weight and liver toxicity with hepatocellular necrosis at 1.7 mg/kg bw and above in the males. The NOAEL was estimated to be 0.56 mg/kg bw/day in males and 22 mg/kg bw/day in females [3, 4].

In a 90 day study in rhesus monkeys, PFOA (0-100 mg/kg bw/day) was given by gavage. All monkeys in the highest dose group died, showing signs of anorexia, swollen face and eyes, reduced body weight, prostration and trembling. Animals given the lower doses had gastrointestinal irritation [3, 4].
Two studies have been carried out in cynomolgus monkeys. The first reported no clinical signs of toxicity or changes in body weight after administration of 20 mg/kg bw/day\(^{-1}\) via oral capsule for 4 weeks. In the second study 30 mg/kg bw/day was given by capsule for 26 weeks. This resulted in reported weight loss, reduced food consumption, increased liver weight and liver toxicity [3, 4].

**Genotoxicity**

**PFOS**
The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) considered the mutagenicity of PFOS and concluded that it had no apparent structural alerts for mutagenicity and that animal studies showed that it was not metabolised [5]. Negative results were obtained in the Ames test, the reverse mutation assay and the *in vitro* chromosomal aberration assay using human whole blood lymphocytes. The *in vitro* UDS assay in rat liver hepatocytes and the mouse bone-marrow micronucleus test were also negative [1, 5]. Overall, the COM considered PFOS as not mutagenic [3, 5].

**PFOA**
The COM considered the mutagenicity of PFOA and concluded that it had no apparent structural alerts for mutagenicity and that animal studies showed that it was not metabolised [4]. PFOA, with and without metabolic activation, was negative in the reverse mutation assay, the mouse bone marrow micronuclei assay and did not induce mutations in the HPRT gene. Overall the COM considered that PFOA was not mutagenic [3, 4].

**Carcinogenicity**

**PFOS**
PFOS has been found to induce tumours of the liver, thyroid and mammary gland in rats given approximately 2 mg/kg bw/day the diet for 104 weeks. The COC concluded that there was equivocal evidence for carcinogenicity (limited to hepatocellular adenoma) of PFOS in animal studies. When considering the COM opinion and the carcinogenicity data it was agreed that it induced carcinogenicity via a non-genotoxic mechanism [3, 5].

**PFOA**
PFOA has been shown to induce Leydig cell adenomas, pancreatic acinar cell adenomas and hepatocellular adenomas in chronic studies in the rat. The COC considered that the Mode of Action (MOA) for the induction of the Leydig cell tumours (activation of aromatase and subsequent increase in serum oestradiol levels) was unlikely to occur in humans. However, it was not possible to propose a MOA for the liver and pancreatic tumours. Therefore the significance of these for humans could not be discounted. For risk assessment purposes it would be acceptable to adopt a threshold approach.

**Reproductive and developmental toxicity**

**PFOS**
Several studies have been carried out in which rats were given up to 10 mg/kg bw/day PFOS by gavage during various stages of gestation. Maternal toxicity was reported at this dose level based on a reduction in body weight and food consumption, hunched position, alopecia and rough coat. Adverse developmental effects were observed including a reduction in implantation sites, loss of viable fetuses as well as an increased incidence of cleft palate and cardiac abnormalities [6, 14]. The NOAEL for not maternal toxicity and effects on development was 1 mg/kg bw/day.
Maternal and developmental studies were also carried out in mice and reported a decreased maternal weight gain after administration of 20 mg/kg bw/day, although the number of implantations or live fetuses was unaffected. Birth defects noted were similar to those reported in the rat, namely cleft palate and cardiac abnormalities. These were primarily seen at the top dose (20 mg/kg bw/day) which was also associated with maternal toxicity. In a similar study in which mice were administered the same dose, neonates from the top dose (20 mg/kg bw/day) became pale and inactive and moribund soon after birth [6, 14]. Some effects on viability were seen at 10 mg/kg bw/day and above.

PFOS (2.5 mg/kg bw/day) given to rabbits during gestation caused a decrease in fetal body weight and fetal malformations, whereas maternal toxicity was reported at 1 mg/kg bw/day [6, 14].

A two generation reproductive study was carried out in rats given up to 3.2 mg/kg bw/day for six weeks prior to and during mating and throughout gestation, parturition and lactation. Overall there were no signs of toxicity, mortality or adverse effects on mating in the F0 generation males or females. At the highest doses (1.6 and 3.2 mg/kg bw/day) viability of the pups was reduced and reversible delays in physical development were observed [6, 14].

**PFOA**

In a two-generation study in rats administered up to 30 mg/kg bw/day by gavage, no effects on reproductive endpoints including mating and fertility were seen. The F1 and F2 generation pups had a decreased body weight at the top dose, although only F1 pups had a reduced viability [6, 15].

In a developmental toxicity study, administration of PFOA (up to 150 mg/kg bw/day) to rats by gavage during gestation reduced maternal body weight but did not affect the reproductive tract of the dams. No developmental toxicity was seen at any dose level [6, 15]. In a developmental toxicity study in rabbits given PFOS by gavage during gestation, a reduction in body weight gain was seen only at the top dose of 50 mg/kg bw/day. The only adverse effects seen on development was a dose related increase in skeletal variations (extra ribs) which was statistically significant only at the top dose of 50 mg/kg bw/day [6].

In a developmental gavage study in mice administered from 1-40 mg/kg bw/day maternal liver weight at term was significantly increased at all dose levels. There were significant increases in the incidence of full litter resorptions and neonatal mortality at 5 mg/kg bw/day and above. No significant increase in malformations was seen at any dose level. The NOAEL for developmental effects was 1 mg/kg bw/day [4].
References


10. Health Protection Agency (HPA), *Maximum acceptable concentrations of perfluorooctane (PFOS) and perfluorooctanoic acid (PFOA) in drinking water.* 2007.


This document from the PHE Centre for Radiation, Chemical and Environmental Hazards reflects understanding and evaluation of the current scientific evidence as presented and referenced in this document.